$-S(O)_2N(R^5)-$, $-N(R^5)S(O)-$, $-N(R^5)S(O)_2-$, $-N(R^5)CON(R^5)-$, $-N(R^5)CSN(R^5)-$, $-N(R^5)SON(R^5)-$, or $-N(R^5)SO_2N(R^5)-$;

R^5 is a hydrogen atom or a straight or branched alkyl group;

r and s, which may be the same or different, is each zero or an integer 1 provided that when r is zero R^1 is an optionally substituted pyridyl group;

Alk^2 is a straight or branched alkylene chain;

m is zero or an integer 1;

R^2 is a hydrogen atom or a methyl group;

X^1 is a group selected from $-N(R^3)CO-$, (where R^3 is a hydrogen atom or a straight or branched alkyl group); $-N(R^3)SO_2-$, $-N(R^3)C(O)O-$ or $-N(R^3)CON(R^{3a})-$ (where R^{3a} is a hydrogen atom or a straight or branched alkyl group);

R^4 is an optionally substituted C_{1-6} aliphatic, C_{3-10} cycloaliphatic or C_{7-10} polycycloaliphatic group;

and the salts, solvates, hydrates and N-oxides thereof.

C2 contd

REMARKS

Claims 1 and 5 to 19 are pending in the present application. Claims 1 and 14 have been amended herein. No new claims have been added and no claims have been canceled.

Reconsideration of the present application in view of the foregoing amendments and the following remarks is requested respectfully.

Discussion of the Rejection Under Section 112, first paragraph

Claim 15 has been rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. The Office Action asserts that "[u]ndue experimentation would be required to make or use the invention based on the content of the disclosure due to the breadth of the claims, the level of predictability in the art of the invention, and the poor amount of direction provided by the inventor." (Office Action dated December 21, 2001, page 2). Applicants respectfully traverse the rejection because the specification enables the skilled artisan to make and use the full scope of the subject matter defined by the claims without undue experimentation.

The enablement requirement is met if the specification enables the skilled artisan to make and use the subject matter defined by the claims without ***undue*** experimentation. *In re Angstadt*, 537 F.2d 498 (C.C.P.A. 1976). Extensive experimentation is often necessary to practice inventions that involve unpredictable technologies, and such experimentation is not undue. *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

The specification enables those of ordinary skill in the art to practice the full scope of the methods defined by claim 15 without undue experimentation. Claim 15 recites methods for the prophylaxis or treatment of diseases or disorders in which inflammation due to leukocyte migration and activation plays a role. As detailed in the specification, the physical interaction of inflammatory leukocytes with other cells is mediated by adhesion molecules found on the surface of leukocytes. (See, for example, page 1, line 4 to page 5, line 8 of the specification as filed). Adhesion molecules, including integrins, bind to ligands present on the surface of other cells, thereby mediating the interaction of leukocytes with other cells.

The integrin termed $\alpha_4\beta_1$ is widely referred to as Very Late Antigen 4 or VLA4. Data obtained using animal models in which monoclonal antibodies were used to inhibit the function of various integrins demonstrate that the interaction between VLA4 and ligands on other cells plays an important role in leukocyte migration and activation. *Id.* Inhibition of the interaction between VLA4 and its ligands blocks leukocyte migration and activation. *Id.*

Numerous diseases involve inflammation due to leukocyte migration and activation, including inflammatory arthritis, multiple sclerosis, allograft rejection, diabetes, inflammatory dermatoses, asthma, and inflammatory bowel disease. *Id.* Inhibition of the interaction between VLA4 and its ligands is useful for the treatment of such diseases and disorders. *Id.* The compounds defined by the present claims are potent and selective inhibitors of the binding of VLA4 to its ligands, and hence are useful for the prophylaxis and treatment of diseases and disorders that involve leukocyte migration and activation. (See page 4, lines 25 to 29 of the specification as filed). The compounds defined by the present claims are thus useful for the prophylaxis or treatment of inflammatory arthritis, multiple sclerosis, allograft rejection, diabetes, inflammatory dermatoses, asthma, and inflammatory bowel disease. (See page 4, line 31 to page 5, line 8 of the specification as filed).

The specification provides abundant guidance regarding how to synthesize the compounds defined by the present claims and how to quantify their potency as integrin inhibitors. For example, the specification describes numerous processes for the synthesis of the compounds defined by the present claims. (See page 16, line 6 to page 22, line 22 of the specification as filed). The specification further provides 36 working examples in which the synthesis of various compounds defined by the claims is described. (See page 16, line 24 to

page 37, line 7 of the specification as filed). In addition, the specification describes assays that can be used to determine the potency and selectivity of the claimed compounds for inhibition of the activity of α4 integrins. (See page 37, line 10 to page 39, line 19 of the specification as filed).

The specification also provides abundant teachings regarding formulation and administration of the compounds defined by the present claims. For example, the specification describes pharmaceutical compositions comprising the claimed compounds and explains that such compositions may be administered orally, bucally, parenterally, nasally, topically or rectally, or may be administered by inhalation or insufflation. (See page 5, line 10 to page 6, line 36 of the specification as filed). The specification further teaches how to formulate the claimed compounds for the various possible modes of administration. *Id.* In addition, the specification describes dosages of the claimed compounds that are suitable for the prophylaxis or treatment of various diseases and disorders. (See page 7, lines 1 to 10 of the specification as filed).

The specification therefore teaches one of ordinary skill in the art how to synthesize the compounds defined by the present claims, and how to determine the inhibitory activity of the compounds. In addition, the specification teaches those of ordinary skill in the art how to formulate pharmaceutical compositions containing the claimed compounds and how to administer such compositions for the prophylaxis or treatment of various diseases and disorders.

Although the Office Action has asserted that "[t]here is no known cure in the art for multiple sclerosis," (Office Action dated April 26, 2001), claim 15 does not recite a method

for *curing* multiple sclerosis, but, rather, recites a method for the *prophylaxis or treatment* of, *inter alia*, multiple sclerosis. Applicants direct the Examiner to the attached Drug Report (enclosed herewith as Appendix A) describing a humanized monoclonal antibody that acts a specific inhibitor of VLA4. The antibody is currently in Phase III clinical trials for the treatment of multiple sclerosis. A VLA4 inhibitor has therefore been shown to be clinically effective for the treatment of multiple sclerosis, demonstrating predictability in the art for the treatment of multiple sclerosis by inhibition of α4 integrins.

Although one of ordinary skill in the art may have to engage in some experimentation to practice the methods of claim 15, such experimentation would not be undue given the guidance provided in the specification and the knowledge of those of ordinary skill in the art. The specification teaches the skilled artisan how to make and use the VLA4 inhibitors defined by the present claims for the prophylaxis and treatment of inflammatory arthritis, multiple sclerosis, allograft rejection, diabetes, inflammatory dermatoses, asthma, and inflammatory bowel disease, and therefore fully enables the methods of claim 15. Applicants accordingly, respectfully request withdrawal of the rejection.

Discussion of the Rejection Under Section 112, Second Paragraph

A. Claims 1 and 14 have been rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite. The Office Action asserts that the terms "substituted aliphatic," "heteroaliphatic chain," "optionally substituted aliphatic," "cycloaliphatic," and "polycycloaliphatic group" in claim 1, and "cycloaliphatic," "aromatic," "heteroaromatic," "polycycloaliphatic," and "polyheterocycloaliphatic" in claim 14 "are so broad that they are

virtually meaningless." (Office Action dated April 26, 2001, page 5). Applicants respectfully traverse the rejection because the cited terminology conveys a clear and definite meaning to those of ordinary skill in the art of organic chemistry, and a skilled artisan would therefore understand the metes and bounds of the claims.

Preliminary, Applicants note that in the amendments made September 25, 2001, the terms "aromatic," "heteroaromatic," and "polyheterocycloaliphatic" were deleted from claim 14.

A fundamental principle of 35 U.S.C. § 112, second paragraph is that "breadth is not to be equated with indefiniteness." *In re Miller*, 441 F.2d 689, 693 (C.C.P.A. 1971); *In re Robins*, 429 F.2d 452, 458 (C.C.P.A. 1970)("[T]he breadth of the claims insofar as the catalyst is concerned is indeed immense. However, 'Breadth is not indefiniteness.'")(citations omitted). A claim that reads on vast numbers of chemical compounds is not rendered indefinite, so long as the boundaries of patent protection sought are clearly set forth. *In re Barr*, 444 F.2d 588, 595 (C.C.P.A. 1971). Accordingly, if those of ordinary skill in the art can determine whether a particular compound is or is not within the scope of a claim, the requirements of the second paragraph of 35 U.S.C. § 112 have been fulfilled, regardless of the breadth of the claim. *In re Miller*, 441 F.2d 689, 693 (C.C.P.A. 1971); *In re Moore*, 439 F.2d 1232 (C.C.P.A. 1971).

Moreover, definiteness of claim language must be analyzed, not in a vacuum, but in light of the content of the particular application disclosure, the teachings of the prior art, and the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. M.P.E.P. § 2173.02.

When the present claims are examined in light of the specification, it becomes apparent that the claims circumscribe the claimed subject matter with a reasonable degree of precision and particularity such that one of ordinary skill in the art of organic chemistry could easily determine whether a particular compound is or is not within the scope of the claim. The terms "aliphatic," "substituted aliphatic," "heteroaliphatic," "cycloaliphatic," and "polyheteroaliphatic" ***are defined in the specification***, and no reason therefore exists to believe that the skilled artisan would have any difficulty in understanding which groups are encompassed by the terms. (See, for example, page 9, line 1 to page 10, line 2 and page 12, line 22 to page 13, line 26 of the specification as filed.) One of ordinary skill in the art could therefore readily determine whether a particular compound falls within the scope of the claims, and could thus determine the metes and bounds of the claims. The claims therefore meet the requirements of the second paragraph of 35 U.S.C. § 112.

Although the Office Action has alleged that the cited terms "are so broad that they are virtually meaningless," (Office Action dated April 26, 2001, page 5), the Office Action has failed to demonstrate that one of ordinary skill in the art would not understand the meaning of the cited terms, and would not understand which groups are encompassed by the cited terms when the claims are read in light of the specification. Accordingly, the rejection for alleged indefiniteness is believed to be improper, and Applicants request withdrawal thereof.

B. Claim 1 has been rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite. The Office Action asserts that the phrase "linker atom or group...is so broad as to render the claim meaningless." (Office Action dated December 21, 2001, page 3).

Without conceding the correctness of the rejection and to further clarify the subject

matter that Applicants regard as their invention, claims 1 and 14 have been amended to recite particular linker atoms or groups. Support for the amendments is found in the specification at, for example, page 8, lines 18 to 26. Applicants submit that the rejection has been obviated, and respectfully request withdrawal thereof.

Discussion of the Markush Objection

Claims 1 and 14 have been objected to as allegedly drawn to an improper Markush group. ***Applicants respectfully repeat their request for clarification of this objection, as the Office Action fails to point out the Markush group that serves as the basis of the objection.*** Applicants requested clarification of this objection in the Request for Reconsideration filed September 25, 2001, and, in the Office Action dated December 21, 2001, the Examiner failed to specify which Markush group serves as the basis of the objection. The Examiner's failure to clarify the basis of the objection is unnecessarily delaying prosecution of the present application. As best understood, the Office Action appears to object generally to the compounds of formula I as allegedly lacking what the Office Action terms a "common nucleus."

Applicants respectfully submit that consideration of the novel phenylalanine derivatives of the present invention *as a whole* reveals that the compounds possess structural similarity and a common utility, and as such, the rejection is misplaced. *In re Harnisch*, 631 F.2d 716, 722 (C.C.P.A. 1980)(stating that "in determining the propriety of a Markush grouping the compounds must be considered as wholes and not broken down into elements or other components."); *In re Jones*, 162 F.2d 479 (C.C.P.A. 1947). Compounds that possess

common nuclei, but also possess side chains in which wide variation exists, may properly be included in a Markush group, as long as the compounds exhibit common properties. *In re Harnisch*, 631 F.2d 716, 722 (C.C.P.A. 1980); *Ex parte Dahlen*, 42 U.S.P.Q. 208 (Bd. App. 1938).

As detailed throughout the specification, the claimed compounds possess a common structural core, namely, that of a phenylalanine derivative. (See, for example, page 3, line 34 to page 4, line 23; page 15, line 28 to page 16, line 4; and pages 25 to 36 of the specification as filed). Moreover, the claimed compounds exhibit a common activity - they are potent and selective inhibitors of α4 integrins. (See, for example, page 3, lines 25 to 29; and page 37, line 10 to page 39, line 19 of the specification as filed). The claimed compounds therefore possess a "community of properties justifying their grouping." *In re Harinsch*, 631 F.2d at 722 (discussing *Ex parte Dahlen*, 42 U.S.P.Q. 208 (Bd. App. 1938)). Thus, to the extent that claims 1 and 14 contain a Markush group, which Applicants do not concede, the group is a proper Markush group because the claimed compounds possess a common structural core and exhibit a common activity. Accordingly, Applicants respectfully request withdrawal of the objection.

Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the Office Action of record. Accordingly, an early and favorable action on the merits is requested respectfully.

Attached hereto is a marked-up version of the changes made to the claims by the

current amendment. The attached page is captioned **"VERSION WITH MARKINGS TO SHOW CHANGES MADE."**

Respectfully submitted,

Date: May 15, 2002

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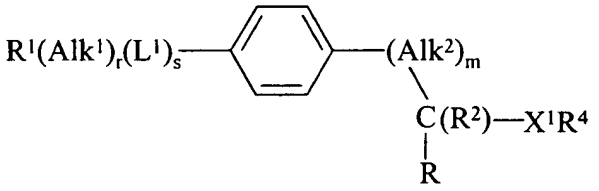
VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 1 and 14 have been amended as follows:

1. (Amended Three Times) A compound of formula (1a):



(1a)

wherein:

R is a carboxylic acid;

R^1 is an optionally substituted pyridyl group;

Alk^1 is an optionally substituted C_{1-6} aliphatic chain or C_{1-6} heteroaliphatic chain containing one, two, three or four heteroatoms or heteroatom-containing groups;

L^1 is ~~a linker atom or group~~ -O-, -S-, -C(O)-, -C(O)O-, -C(S)-, -S(O)-, $-S(O)_2-$, $-N(R^5)-$, $-CON(R^5)-$, $-OC(O)N(R^5)-$, $-CSN(R^5)-$, $-N(R^5)CO-$, $-N(R^5)C(O)O-$, $-N(R^5)CS-$, $-S(O)N(R^5)-$, $-S(O)_2N(R^5)-$, $-N(R^5)S(O)-$, $-N(R^5)S(O)_2-$, $-N(R^5)CON(R^5)-$, $-N(R^5)CSN(R^5)-$, $-N(R^5)SON(R^5)-$, or $-N(R^5)SO_2N(R^5)-$;

R^5 is a hydrogen atom or a straight or branched alkyl group;

r and s, which may be the same or different, is each zero or an integer 1;

Alk^2 is a straight or branched alkylene chain;

m is zero or an integer 1;

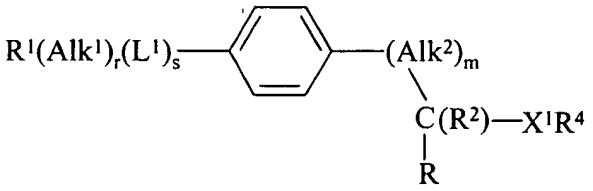
R^2 is a hydrogen atom or a methyl group;

X^1 is a group selected from -N(R^3)CO-, (where R^3 is a hydrogen atom or a straight or branched alkyl group); -N(R^3) SO_2-, -N(R^3)C(O)O- or -N(R^3)CON(R^{3a})- (where R^{3a} is a hydrogen atom or a straight or branched alkyl group);

R^4 is an optionally substituted C_{1-6} aliphatic, C_{3-10} cycloaliphatic or C_{7-10} polycycloaliphatic group;

and the salts, solvates, hydrates and N-oxides thereof.

14. (Amended Twice) A method for the prophylaxis or treatment of a disease or disorder involving inflammation in which the extravasation of leukocytes plays a role in a mammal, which comprises administering to a mammal suffering from such a disease or disorder a therapeutically effective amount of a compound of formula (1):



(1)

wherein:

R is a carboxylic acid (CO_2H);

R^1 is a hydrogen atom or a hydroxyl, straight or branched alkoxy or optionally

substituted pyridyl group;

Alk^1 is an optionally substituted C_{1-6} aliphatic chain or C_{1-6} heteroaliphatic chain containing one, two, three or four heteroatoms or heteroatom-containing groups;

L^1 is ~~a linker atom or group~~ -O-, -S-, -C(O)-, -C(O)O-, -C(S)-, -S(O)-, $-S(O)_2-$, $-N(R^5)-$, $-CON(R^5)-$, $-OC(O)N(R^5)-$, $-CSN(R^5)-$, $-N(R^5)CO-$, $-N(R^5)C(O)O-$, $-N(R^5)CS-$, $-S(O)N(R^5)-$, $-S(O)_2N(R^5)-$, $-N(R^5)S(O)-$, $-N(R^5)S(O)_2-$, $-N(R^5)CON(R^5)-$, $-N(R^5)CSN(R^5)-$, $-N(R^5)SON(R^5)-$, or $-N(R^5)SO_2N(R^5)-$;

R^5 is a hydrogen atom or a straight or branched alkyl group;

r and s, which may be the same or different, is each zero or an integer 1 provided that when r is zero R^1 is an optionally substituted pyridyl group;

Alk^2 is a straight or branched alkylene chain;

m is zero or an integer 1;

R^2 is a hydrogen atom or a methyl group;

X^1 is a group selected from $-N(R^3)CO-$, (where R^3 is a hydrogen atom or a straight or branched alkyl group); $-N(R^3)SO_2-$, $-N(R^3)C(O)O-$ or $-N(R^3)CON(R^{3a})-$ (where R^{3a} is a hydrogen atom or a straight or branched alkyl group);

R^4 is an optionally substituted C_{1-6} aliphatic, C_{3-10} cycloaliphatic or C_{7-10} polycycloaliphatic group;

and the salts, solvates, hydrates and N-oxides thereof.